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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,050	08/20/2001	Clifford Charles Shone	1581.0800000	8265

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,050	SHONE ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-43* is/are pending in the application.

4a) Of the above claim(s) *26-28,34,35 and 37-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,29-33,36, 42,43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *25-43* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicant's election of Invention I, (claims 25, 29-33, 36 and 43) in Paper No. 9 is acknowledged. In addition, Applicant pointed to the fact that Claim 42 was not included with any group and appears to be a member of Group I. The examiner agrees that Claim 42 should be a member of Group I and will examine the claims accordingly. Applicant traversed the restriction requirement by first arguing against the reference that was used to dispute Unity of Invention under PCT Rule 13.1 (Figueiredo, et al, 1997, Exper. Neurol., 145: 546-554), suggesting that the superoxide dismutase/tetanus toxin used in that reference is different from that in Claim 1 of the instant Application, because Claim 1 recites a "cleavable" linker. However, the linker used by Figueiredo, et al is *Gly-Pro-Gly*, a peptide that is clearly *cleavable* by several naturally-occurring peptidases (for example: prolyl-endopeptidase), as well as by strong acids. Applicant also disputed the claim groupings in general, arguing that groups I, II, IV and V should not be separated based on differences in structure and function. However, Inventions I, II, IV and V were restricted by the examiner primarily in terms of the *targeting* component of the superoxide dismutase composition, rather than to each SOD/targeting construct (represented, for example, by SEQ ID NO: 1-9), because the targeting sequences are shown to be different and can be each added to a bacterial or human SOD to change its function as claimed. Applicant pointed out that claim 29 is found in Groups I and II, and that this appears to contradict the groupings of claims. Claim 29, depending upon which claim it depends from

and how it is interpreted, can be a bacterial SOD with either targeting component attached. Similarly, Claim 36 can be included in Invention I because the composition recited can be a superoxide dismutase molecule linked, as stated, to a neuronal targeting component. Applicant also disputed the groupings in which polypeptides and polynucleotides were separated, arguing that the search for the polypeptides of Group II would necessarily reveal the polynucleotides encoding them, such as those in Group V. However, Inventive Groups II and V in question were properly restricted as independent and distinct products having characteristic differences in structure and function and having different uses as noted in Paper 8 (11 April 2003). Likewise, the polypeptides of Invention II can be obtained from sources other than from Invention V, such as isolated from natural sources. In addition, a search of the prior art on the polynucleotide will sometimes, *but not always*, reveal prior art relevant to the polypeptide. Finally, since a complete search of the art includes a search of the art that renders an invention obvious as well as anticipatory, the additional searches required for examination of Invention II *with* Invention V would be extensive, thus presenting an undue burden for the examiner. This last point is particularly relevant to the instant Application, since specific SEQ ID NO's are not recited in the claims. Therefore, the claimed proteins encompass a large number of possible proteins and encoding nucleic acids.

Claims 26-28, 34, 35 and 37-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 25, 29-33, 36, 42 and 43 are under examination in the Instant Application.

Informalities

Specification

Brief Description

It is not precisely clear where the figures are described in the Specification. The captions for figures should be in a separately-labeled section called: "Brief Description of the Several Views of the Drawing(s)" and should be a reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74. See MPEP § 608.01(f).

Figures

Figure 1 is objected to because it is not clear from the figure or from the specification what is being measured, and such information is crucial to an understanding of the claimed invention. More specifically, it is not clear how absorbance is related or correlated to the measured independent variable of oxidative protection. Corrections will be required in the event there are allowable claims, however the Applicant is cautioned about adding *new matter* to the Specification.

Sequence Rules

The instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825, because each disclosure of a sequence embraced by the definitions set forth in the rules is

not accompanied by the required reference to the relevant sequence identifier (i.e., SEQ ID NO:). This occurs throughout the disclosure, but see for examples: p. 13, lines 22-29 and Figure 1. Appropriate correction is required.

Claim Rejections/Objections

Claim Rejections - 35 USC § 112, first paragraph, enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 25, 29-33, 36, 42 and 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein the recited composition of superoxide dismutase is delivered to neuronal cells or translocated into neuronal cells, or for the limitations of the claims wherein the composition protects cells against oxidative damage.

Claims 25, 29-33, 36, 42 and 43 are directed to a composition comprising superoxide dismutase (SOD) attached to a large fragment of a *Clostridium* toxin, such as tetanus or botulinum. Furthermore, the claims recite compositions of SOD and *Clostridium* toxins that

bind specifically to neuronal cells and that translocate the composition *into* neuronal cells. Additional dependent claims recite compositions for treating oxidative damage of neuronal cells.

The specification teaches a composition comprising superoxide dismutase (SOD) attached to a fragment of a *Clostridium* toxin, for the purpose of translocating the SOD into neuronal cells and thus protecting them from oxidative damage. However, the disclosure is not enabling for use of the composition to translocate SOD into neuronal cells and reduce oxidative stress. Experiments are described in which the SOD composition is applied to NG-108 neuroblastoma cells both with and without the superoxide generator duroquinone (See Figure 5). Measurements were made that Applicants contend demonstrate protective effects on the cells against superoxide-induced oxidative stress. However, the methods were not described in sufficient detail to enable one skilled in the art to determine the protective effects of the SOD composition on oxidative stress in neuronal cells in the manner described. It is not known, for example, how absorbance of light at 570nm is related to oxidative stress. Nor is it known if the SOD composition was translocated into the cells. It is not known if NG-108 cells are neuronal cells in the sense, for example, of whether they have receptors for Clostridium toxins. Furthermore, the treatment groups seem indistinguishable from each other and there appears to be no concentration effect of superoxide dismutase on the measured variable; SOD at zero concentration had approximately the same effect at a concentration of 100.

Therefore, there is no evidence presented demonstrating a protective effect of the SOD composition on neuronal cells. Nor is there evidence that SOD was translocated into cells.

In addition, the specification is not enabling for the limitations of the claims wherein the recited composition of superoxide dismutase is used to deliver a *therapeutic* agent to neuronal

cells, or used as a *pharmaceutical* composition for reducing oxidative damage in neuronal cells. There is no evidence presented demonstrating a protective effect of the SOD composition on neuronal cells, such that the composition can be used therapeutically to protect cells under physiologically oxidizing conditions, such as such as stroke/reperfusion injury, Parkinson's disease, etc (Specification, page 8).

Due to the large quantity of experimentation necessary: 1) to measure oxidative damage in neuronal cells; 2) to inhibit oxidative damage in neuronal cells using the claimed SOD composition; 3) to overcome the lack of direction/guidance presented in the specification regarding above; 4) to overcome the complex nature of the invention; 5) to overcome the unpredictability of the art; and, 8) to overcome the breadth of the claims which embrace using many possible SOD/*Clostridium* toxin compositions, not all of which can be expected to function in similar ways--undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 30 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 30 and 31 recite an SOD composition comprising fragments, variants and derivatives of the composition that retain neuronal cell binding activity.

The specification teaches a SOD/*Clostridium* toxin composition. However, the specification does not teach functional or structural characteristics of *Clostridium* toxin fragments that retain neuronal cell binding activity. The description of several SOD/*Clostridium* toxin compositions, comprising large known subunits of *Clostridium* toxins is not adequate written description of an entire genus of functionally equivalent polypeptide fragments.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the compositions referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed *Clostridium* toxin fragments, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the polypeptide is part of the invention and reference to a potential method of isolating or producing it. The protein itself is required. See *Fiers v. Revel*, 25

USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a *Clostridium* toxin subunit, comprising well-known neuronal cell binding capability, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 25 and 36 are rejected under 35 U.S.C. 102(b) as being unpatentable over Figueiredo, et al (1997, Exp. Neurol., 145: 546-554). Figueiredo et al. disclose a superoxide dismutase/tetanus toxin composition which is indistinguishable from the composition recited in Claims 1 and 36. This reference meets the limitation of Claims 1 and 36 of "a SOD linked by a cleavable linker to a neuronal cell targeting component" and a "therapeutic agent linked by a

cleavable linker to a neuronal cell targeting component," the cleavable linker being an unspecified short polypeptide in Claims 1 and 36 of the instant Application. One way to distinguish the claimed invention from the prior art is to recite SEQ ID NOs for each composition of SOD and *Clostridium* toxin.

Likewise, Claims 25 and 36 are also rejected under 35 U.S.C. 102(b) as being unpatentable over Francis, et al (1995, J. Biol. Chem., 270(25): 15434-15442). Francis, et al disclose a superoxide dismutase/tetanus toxin composition (SOD:Tet451) which is indistinguishable from the composition recited in Claims 1 and 36. This reference meets the limitation of Claims 1 and 36 of "a SOD linked by a cleavable linker to a neuronal cell targeting component" and a "therapeutic agent linked by a cleavable linker to a neuronal cell targeting component.

Conclusion: Claims 25, 29-33, 36, 42 and 43 are rejected for the reasons specified above.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (703) 308-9346. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SLW

7/28/03

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER